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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,913	12/17/2001	Peter Beyer		5922

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SYNGENTA BIOTECHNOLOGY, INC.
PATENT DEPARTMENT
3054 CORNWALLIS ROAD
P.O. BOX 12257
RESEARCH TRIANGLE PARK, NC 27709-2257

EXAMINER	
KALLIS, RUSSELL	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,913	BEYER ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/05/2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-23, in the reply filed on May 26, 2004 is acknowledged.

Claims 1-30 are pending. Claims 24-30 are withdrawn. Claims 1-23 are examined.

Drawings

The drawings are objected to because figures 1, 2, and 3 are labeled by hand and not by machine or computer text, the use of fig. or figure is inconsistent, and the use of Figure 4/5 and then Figure 5 is inconsistent. Corrected drawing sheets are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims one or more plant expression cassettes capable of directing expression of two or three enzymes comprising nucleotide sequences encoding phytoene synthase from plants, and phytoene desaturase from bacteria or fungi; phytoene synthase from fungi, and phytoene desaturase from fungi or bacteria; or phytoene synthase from plants or fungi, and phytoene desaturase and zeta carotene desaturase from plants; and transgenic plant cells and plants comprising said expression cassettes; and a method of transforming a plant or plant cell.

Applicant disclose expression cassettes comprising nucleotide sequences encoding a plant phytoene synthase from daffodil (*Narcissus pseudonarcissus*) and a bacterial phytoene desaturase from *Erwinia eurodova* (Plasmid A on pages 21-22), and a plant lycopene cyclase from daffodil (*Narcissus pseudonarcissus*) (Plasmid B on page 23); and in the specification provides reference to a plant phytoene synthase polynucleotide sequence from tomato on page 4, lines 2-3; to bacterial phytoene desaturase polynucleotides on page 3, lines 25-29.

Applicant does not describe nucleotide sequences encoding phytoene synthase and phytoene desaturase from plants other than phytoene synthase from daffodil (*Narcissus pseudonarcissus)* and tomato; or any nucleotide sequences encoding phytoene synthase or phytoene desaturase from fungi; or any nucleotide sequences encoding phytoene desaturase and zeta carotene from plants.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. The court stated that, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Applicants fail to describe a representative number of expression cassettes comprising nucleotide sequences encoding phytoene synthase from plants, and phytoene desaturase from fungi; phytoene synthase from fungi, and phytoene desaturase from fungi; or phytoene synthase from plants or fungi, and phytoene desaturase and zeta carotene desaturase from plants falling within the scope of the claimed genera of nucleotide sequences. Applicants only describe expression cassettes comprising nucleotide sequences encoding a plant phytoene synthase from daffodil (*Narcissus pseudonarcissus*) and a bacterial phytoene desaturase from *Erwinia eurodova* (Plasmid A on pages 21-22), and a plant lycopene cyclase from daffodil (*Narcissus pseudonarcissus*) (Plasmid B on page 23); and in the specification provides reference to a tomato plant phytoene synthase polynucleotide sequence on page 4, lines 2-3; and to bacterial phytoene desaturase polynucleotides on page 3, lines 25-29.

Further, Applicants fail to describe structural features common to members of the claimed genera of polynucleotides. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Since the genera of nucleotide sequences encoding phytoene synthase from plants, and phytoene desaturase from fungi; phytoene synthase from fungi, and phytoene desaturase from fungi; or phytoene synthase from plants or fungi, and phytoene desaturase and zeta carotene desaturase from plants has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims drawn to expression cassettes comprising nucleotide sequences encoding a plant phytoene synthase from daffodil or tomato and a bacterial phytoene desaturase, or a plant phytoene synthase from daffodil or tomato, a bacterial phytoene desaturase, and a plant lycopene cyclase from daffodil; and methods of transforming plant cells and plants therewith, and transformed plant cells and plants thereof; does not reasonably provide enablement for claims drawn to expression cassettes comprising nucleotide sequences encoding phytoene synthase from plants, and phytoene desaturase from fungi; phytoene synthase from fungi, and phytoene desaturase from fungi; or phytoene synthase from plants or fungi, and phytoene desaturase and zeta carotene desaturase from plants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by

one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are broadly drawn to one or more plant expression cassettes capable of directing expression in plant cells of two or three enzymes comprising nucleotide sequences encoding phytoene synthase from plants, and phytoene desaturase from bacteria or fungi; phytoene synthase from fungi, and phytoene desaturase from fungi or bacteria; or phytoene synthase from plants or fungi, and phytoene desaturase and zeta carotene desaturase from plants; transgenic plant cells and plants comprising said expression cassettes; and methods of transforming plants and plant cells therewith.

Applicant discloses expression cassettes comprising nucleotide sequences encoding a plant phytoene synthase from daffodil (*Narcissus pseudonarcissus*) and a bacterial phytoene desaturase from *Erwinia eurodova* (Plasmid A on pages 21-22), and a plant lycopene cyclase from daffodil (*Narcissus pseudonarcissus*) (Plasmid B on page 23); and in the specification provides reference to a plant phytoene synthase polynucleotide sequence from tomato on page 4, lines 2-3; to bacterial phytoene desaturase polynucleotides on page 3, lines 25-29; Applicant provides guidance for construction of plasmid A and B and *Agrobacterium* mediated transformation of rice on pages 21-24, and report that the seeds from the transformed rice plants comprising plasmid A (figure 3B), or plasmid A and B (figure 3C) contain β-carotene (provitamin A) and other carotenoids on page 25.

Applicants fail to teach polynucleotides encoding phytoene synthase and phytoene desaturase from fungi; or transformed plant cells and plants comprising polynucleotides encoding a phytoene synthase and a phytoene desaturase from fungi together, or in combination with a phytoene synthase polynucleotide from plants, a phytoene desaturase polynucleotide from bacteria, or a zeta carotene desaturase polynucleotide from plants, wherein the seeds from the transformed plants contain β-carotene (provitamin A) and other carotenoids, and methods of transforming plants and plant cells therewith.

The state-of-the-art is such that one of skill in the art could not predict whether polynucleotides encoding fungal phytoene synthases or phyotene desaturases when isolated and transformed into a plant or plant cell would transcribe a message encoding an active enzyme in a plant or plant cell. The cloning of unexpected cDNA showed that fungal carotenoid genes transcribe mRNA that is alternatively spliced, apparently regulated by cellular conditions, producing either productive or unproductive forms of mRNA. (Lodato P. *et al.*, Applied and Environmental Microbiology, August 2003; Vol. 69, No. 8; pp. 4676-4682; see abstract; and Results beginning on page 4678, column 2 to page 4679 end of column 2). Further, one of skill in the art could not predict that the P domain of the fungal *carRP* gene from *M. circinelloides*, comprising the coding region for both encodes the lycopene cyclase (R domain) and phytoene synthase (P domain), would require the R domain for P domain's phytoene synthase activity and thus, present unexpected problems when attempting to engineer carotenoid biosynthesis in a plant using fungal sequences. (Velayos A. *et al.*, Eur. J. Biochem. 2000, Vol. 267; pp. 5509-5519; see abstract and page 5517, column 2 lines 20-25).

Moreover, the state of the art for isolating and using phytoene synthase encoding polynucleotides from plants, or any other of the claimed encoding polynucleotides carotenoid biosynthetic enzymes from plants, is unpredictable because so few of the genes had been isolated and studied. The existence of an isoform of phytoene synthase (*PSY2*) in tomato was not known and escaped immediate characterization because the primary sequence and the expression pattern was different from the known phytoene synthase sequence (*PSY1*) and led to its' designation as a pseudogene (Bartley G. *et al.*, The Journal of Biological Chemistry, December 5, 1993; Vol. 268, No. 34; pp. 25718-25721; see abstract and page 25718, column 2 lines 1-9). Furthermore, an RT-PCR analysis of the level of phytoene synthase expression compared the tomato *psy1* mutant and tomato *psy1* antisense plants and showed *psy2* (an isoform of *psy1*) expression in tomato fruits, but with at least a 100 fold reduction in phytoene as measured by HPLC; indicating that although *psy2* was expressed in the tomato fruit it did not result in production of phytoene. Further analysis of *in vitro* production of phytoene from tomato fruit extracts of the *psy1* mutant and *psy1* antisense tomatoes indicated that the extracts are capable of producing phytoene when fed free GGPP substrate (C14 labeled), strongly suggesting the *psy1* enzyme participates in specific metabolic channeling in fruit tissues and that *psy2* does not function to produce phytoene in fruit tissues because it can not participate in an apparent carotenoid producing protein complex that requires isoform specific protein-protein interactions (Fraser P. *et al.*, Plant Molecular Biology, 1999; Vol. 40, pp. 687-698; see abstract, figures 2-3; page 691, column 2 lines 4-12; and page 696, column 2 to page 697 column 1, line 9).

Given the lack of guidance in the instant specification, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the

multitude of non-exemplified mRNA sequences, isolating or amplifying non-functional transcripts or isoforms, producing expression vectors and transforming plants therewith, in order to identify those polynucleotides that when expressed, in combination with other heterologous polynucleotides encoding other carotenoid biosynthetic enzymes, result in the production of active phytoene synthase, phytoene desaturase, and zeta carotene desaturase enzymes or enzyme complexes and result in plants with increased carotenoids or provitamin A.

Therefore, given the breadth of the claims; the lack of guidance and working examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled throughout the broad scope of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burkhardt P. *et al.*, in RICE GENETICS III; Proceeding of the Third International Rice Genetics Symposium; International Rice Research Institute (IRRI), 1996; Khush G. S. ed., in view of Bramley P. M., Pure and Appl. Chem., 1997; Vol. 69, No. 10; pp. 2159-2162, in further view of Bartley G. E., *et al.*, Eur. J. Biochem., January 1999; Vol. 259, pp. 396-403.

The claims are broadly drawn to one or more plant expression cassettes capable of directing expression of two or three enzymes comprising nucleotide sequences encoding

phytoene synthase from plants, and phytoene desaturase from bacteria or fungi; phytoene synthase from fungi, and phytoene desaturase from fungi or bacteria; or phytoene synthase from plants or fungi, and phytoene desaturase and zeta carotene desaturase from plants; transgenic plant cells and plants comprising said expression cassettes; and methods of transforming plants and plant cells therewith.

Burkhardt teaches a method of transforming rice plants (*Liliopsida*) with DNA molecules capable of expressing in plant cells consisting of a phytoene synthase and phytoene desaturase from daffodil, using either the CaMV35S or the endosperm tissue specific rice *Gt1* promoter, and the *hpt* hyrgomycin antibiotic selection gene under control of a constitutive promoter (page 819, lines 27-44); that rice milled endosperm has virtually no beta-carotene (page 818, lines 9-11); the availability of genes encoding the four necessary enzymes for beta-carotene biosynthesis in plants and bacteria (page 819, lines 16-22); and the accumulation of high levels of phytoene in the seeds of several lines of transformed rice plants (page 820, lines 1-2).

Burkhardt does not teach a bacterial phytoene desaturase encoding sequence fused to a sequence encoding the pea Rubisco small subunit transit peptide; a vector encoding system derived from *Agrobacterium tumefaciens*; or a plant transformed with a bacterial phytoene desaturase encoding sequence; or a zeta carotene encoding sequence from a plant.

Bramley teaches a bacterial phytoene desaturase encoding sequence fused to a sequence encoding the pea Rubisco small subunit transit peptide and a plant transformed with a bacterial phytoene desaturase encoding sequence fused to a sequence encoding the pea Rubisco small subunit transit peptide (pages 2160 and 2161, Phytoene desaturase *CrtI* sections); and a vector encoding system derived from *A. tumefaciens* (page 2160, Phytoene synthase section).

Bartley teaches a zeta carotene encoding sequence from a plant (See Abstract lines 1-3 and the first two paragraphs of the Results section).

It would have been obvious at the time of invention to modify the invention of Burkhardt to include the polynucleotide encoding the *Erwinia uredova* bacterial phytoene desaturase and the vector encoding system derived from *A. tumefaciens* of Bramley, or to further include the polynucleotide encoding the *Arabidopsis* plant zeta carotene of Bartley. One of skill in the art would have been motivated by the teachings of Burkhardt that the genes encoding the enzymes required for beta-carotene biosynthesis from plants and bacteria are available in the art, as also taught by Bramley, Bartley, and Applicant's specification; and that rice endosperm contains GGPP the substrate for phytoene synthase, and is thus a valuable tool for engineering provitamin A production, and by the success of Burkhardt in transforming rice with phytoene synthase (daffodil) and phytoene desaturase (daffodil) and expressing the plant phytoene synthase (daffodil) in the endosperm of rice seeds resulting in high levels of phytoene; by the success of Bramley in transforming tomato with bacterial phytoene desaturase (*Erwinia uredova*) resulting in the accumulation of beta-carotene in ripe fruit; and by the success of Bartley in expressing plant zeta carotene desaturase (*Arabidopsis*) in *E. coli* to produce lycopene; that one would have had a reasonable expectation of success in transforming a rice plant with a plant phytoene synthase and a bacterial phytoene desaturase; or a plant phytoene synthase, a plant phytoene desaturase, and a plant zeta carotene desaturase; and producing provitamin A or beta carotene in the endosperm of rice.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Russell Kallis

Russell Kallis Ph.D.
July 16, 2004